77170

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the European patent application described on the following page, as originally filed.	Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03251046.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03251046.3
Demande no:

Anmeldetag:
Date of filing: 21.02.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

UNILEVER PLC
Unilever House,
Blackfriars
London EC4P 4BQ
GRANDE BRETAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Composition

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/ Classification internationale des brevets:

A61K7/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

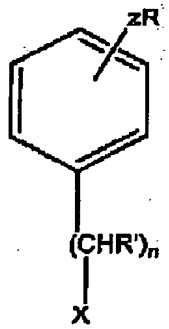
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR LI

COMPOSITION

The present invention relates to an oral composition comprising a novel antibacterial compound.

We have found that there exists a range of compounds which exhibit surprisingly high antibacterial efficacy and are not disclosed for use in oral compositions in the prior art.

Accordingly, the invention provides an oral composition comprising a compound of Formula 1:



Formula (1),

wherein:

R is a group independently selected from the group consisting of: H, F, Cl, Br, -OH, C_1-$_5$ alkyl, -C(O)H, -C(O)C_{1-5} alkyl, -OCH_3, -C_2H_5, -NH_2, -NHC(O)CH_3 and C(O)OC_{1-6} alkyl and z is from 1 to 5;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from $-C(O)-NH-R''$, $-R''$, $-C(O-R'',-C(O)O-R''$, $-O-R''$, $-SO_2NH-R''$, $-OCHR'O-R''$ and $-SO_2-R''$; and R'' is selected from the group consisting of: $-C_{1-16}$ alkyl or $-CH_2C_6H_6$,

and wherein the compound of formula 1 is not a C_{1-16} alkoxy ester of monohydroxybenzoic acid with the hydroxyl group in the para position.

In a preferred embodiment X is $-C(O)O-R''$, wherein R'' is a substituted or unsubstituted branched or straight chain hydrocarbon moiety comprising from 1 to 16 and especially from 5 to 10 carbon atoms. Examples of suitable R'' groups include pentyl, hexyl, benzyl, heptyl, octyl, 2-ethyl hexyl, nonyl, decyl, undecyl, dodecyl and tridecyl. Of these the most preferred are the straight chain alkyls. The most preferred active is where R'' is n-octyl.

According to Formula 1 z is from 1 to 5 and can be any number in between.

According to Formula 1 R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

Manufacture of such compounds as represented by Formula 1 would be a simple step for the man skilled in the art to carry out.

The most preferred antimicrobial agents include 1-(4-Hydroxyphenyl)nonan-1-one.

The compound according to Formula 1 is preferably present in an amount such that an antibacterial effect can be provided. In practice this ranges from 0.05 to 30% by weight of the composition according to the invention. Preferably, in an amount ranging from 0.2 to 10% by weight and even more preferably from 0.1 to 3.5% by weight.

The composition according to the invention may also comprise a divalent metal salt. Preferably, the divalent metal salt is a salt selected from the group consisting of zinc- and stannous salts such as zinc citrate, zinc sulphate, zinc glycinate, sodium zinc citrate, stannous pyrophosphate and mixtures thereof. The preferable divalent metal salt is zinc citrate.

Suitably, the amount of divalent metal salt ranges from 0.01 to 10% by weight of the composition, preferably from 0.05 to 5% by weight, more preferably from 0.1 to 2% by weight and especially preferably from 0.3 to 0.9% by weight of the composition.

The oral composition according to the main claim also preferably comprises Triclosan at from 0.1 to 0.5% by weight of the composition.

The oral composition according to the invention comprise further ingredients which are common in the art, such as:

antimicrobial agents, e.g. Triclosan, chlorhexidine, sanguinarine extract, metronidazole, quaternary ammonium compounds, such as cetylpyridinium chloride; bis-guanides,

such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; and halogenated bisphenolic compounds, such as 2,2' methylenebis-(4-chloro-6-bromophenol);

anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc.;

anti-caries agents such as sodium- and stannous fluoride, aminefluorides, sodium monofluorophosphate, sodium trimeta phosphate and casein;

plaque buffers such as urea, calcium lactate, calcium glycerophosphate and strontium polyacrylates;

vitamins such as Vitamins A, C and E;

plant extracts;

desensitising agents, e.g. potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate and strontium salts;

anti-calculus agents, e.g. alkali-metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates and phosphocitrates etc.;

biomolecules, e.g. bacteriocins, antibodies, enzymes, etc.;

flavours, e.g. peppermint and spearmint oils;

proteinaceous materials such as collagen;

preservatives;

opacifying agents;

colouring agents;

pH-adjusting agents;

sweetening agents;

pharmaceutically acceptable carriers, e.g. starch, sucrose, water or water/alcohol systems etc.;

surfactants, such as anionic, nonionic, cationic and zwitterionic or amphoteric surfactants;

particulate abrasive materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, including agglomerated particulate abrasive materials, usually in amounts between 3 and 60% by weight of the oral care composition.

humectants such as glycerol, sorbitol, propyleneglycol, xylitol, lactitol etc.;

binders and thickeners such as sodium carboxymethyl-cellulose, xanthan gum, gum arabic etc. as well as synthetic polymers such as polyacrylates and carboxyvinyl polymers such as Carbopol®;

polymeric compounds which can enhance the delivery of active ingredients such as antimicrobial agents can also be included;

buffers and salts to buffer the pH and ionic strength of the oral care composition; and

other optional ingredients that may be included are e.g. bleaching agents such as peroxy compounds e.g. potassium peroxydiphosphate, effervescing systems such as sodium bicarbonate/citric acid systems, colour change systems, and so on.

Liposomes may also be used to improve delivery or stability of active ingredients.

The oral compositions may be in any form common in the art, e.g. toothpaste, gel, mousse, aerosol, gum, lozenge, powder, cream, etc. and may also be formulated into systems for use in dual-compartment type dispensers. Preferably the oral composition is suitably packaged and identified as a composition suitable for use in the oral cavity.

Embodiments according to the invention shall now be discussed with reference to the following non-limiting examples.

EXAMPLE 1

(1) 3-hydroxy benzoic acid octyl ester
(2) 2-hydroxy benzoic acid octyl ester [6969-49-9]

(3) 4-Hydroxy-N-octyl benzamide

(4) Octyl-3,5-dihydroxybenzoate

(5) Octyl-4,6-dihydroxybenzoate [37622-46-1]

(6) Octyl-2,6-dihydroxybenzoate

(7) 4-Hydroxy-3,5-dimethoxybenzoic acid octyl ester

(8) 4-Hydroxy-3-methoxybenzoic acid octyl ester [5438-62-0]

(9) 4-Hydroxy-3-chlorbenzoic acid octyl ester [40664-24-2]

(10) Octyl gallate [1034-01-1]

(11) Octyl-3,4-dihydroxybenzoate

(12) 4-Hydroxyphthalic acid dibutylester

(13) 1-(4-Hydroxyphenyl)nonan-1-one [14329-69-9]

(14) 4-Octyloxyphenol [3780-50-5]

(15) 4-Octylphenol [1806-26-4]

(16) 4-hydroxy-N-octyl benzene sulphonamide

(17) (4-Hydroxyphenyl)acetic acid octyl ester

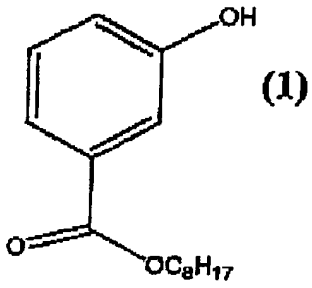
(18) octyl(4'-hydroxyphenoxy) acetate [134447-04-4]

(19) 3,4-Dichloro-2-hydroxy-N-octylbenzene sulphonamide

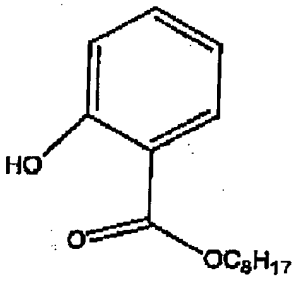
(20) 4-N-acetylamino-N'-octylbenzene sulphonamide

(21) 4-Amino-N-octylbenzene sulphonamide [67491-89-8]

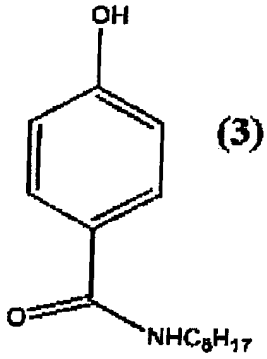
(22) 4-Methoxy-N-octylbenzene sulphonamide


OH
O
OC8H17

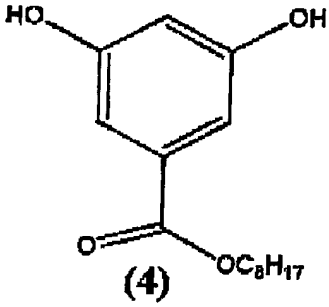
(1)


HO
O
OC8H17

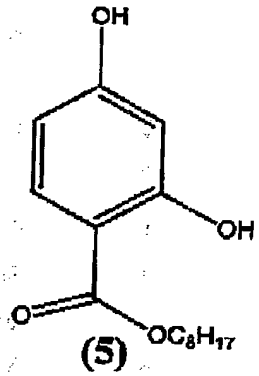
(2)


OH
O
NHC8H17

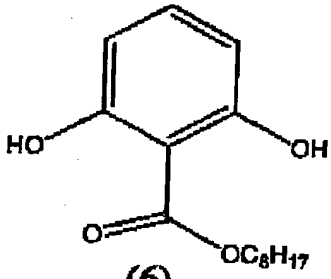
(3)


HO
OH
O
OC8H17

(4)

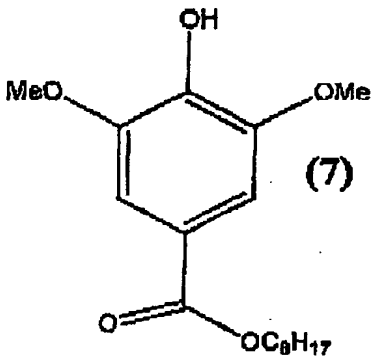

OH
OH
O
OC8H17

(5)

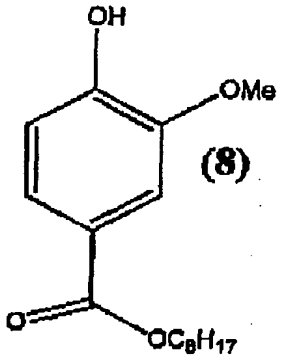

HO
OH
O
OC8H17

(6)

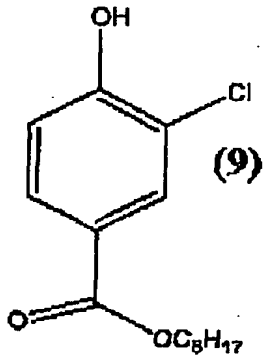
5



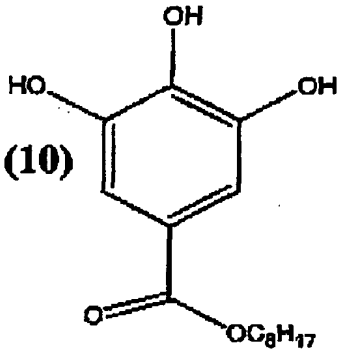
(7)



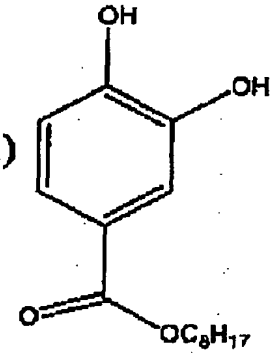
(8)



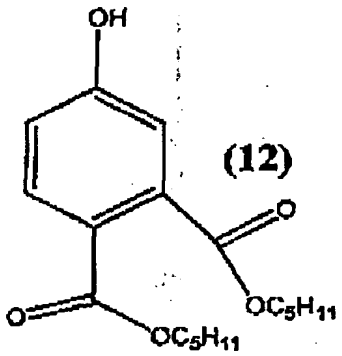
(9)



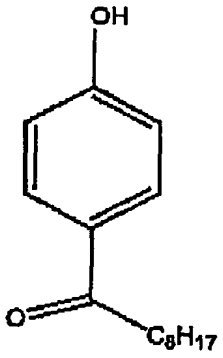
(10)



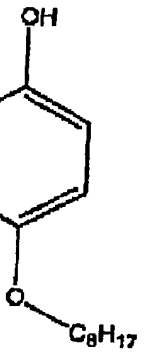
(11)



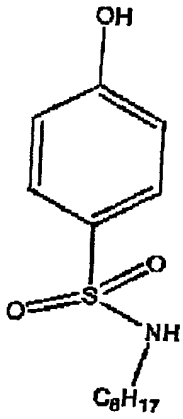
(12)



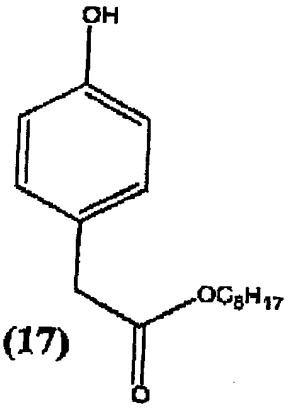
(13)

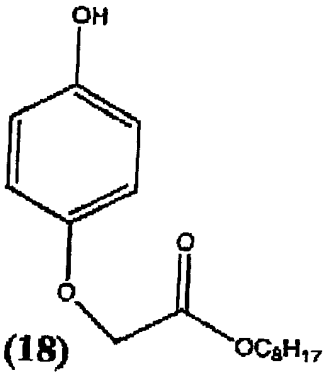
(14) 

(15) 

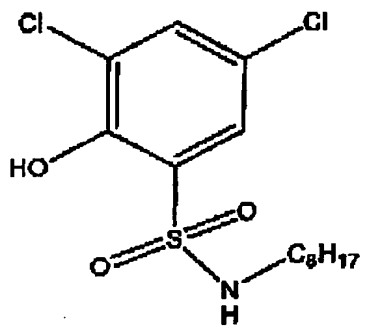
 (16)

5

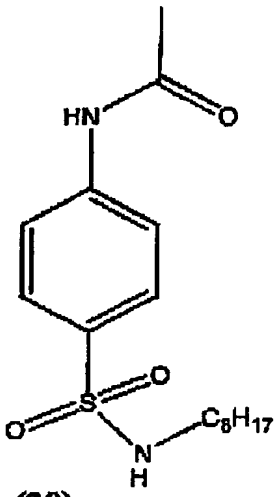
 (17)

 (18)

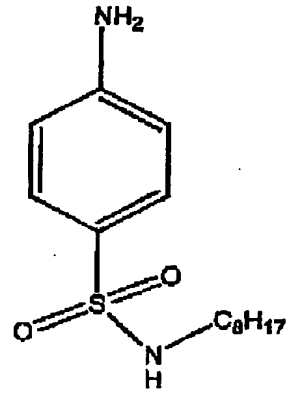
10



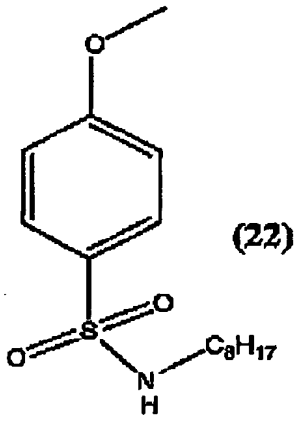
(19)



(20)



(21)



(22)

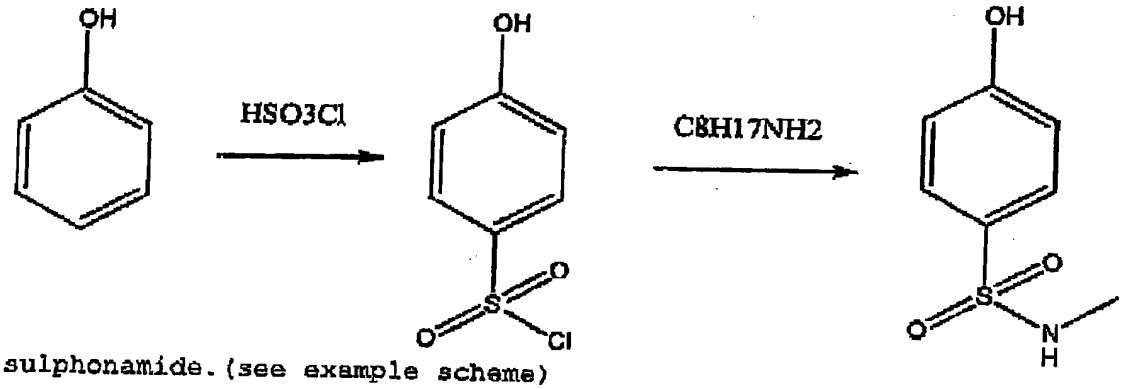
EXAMPLE 2

For compounds 1-12 the synthesis starts from the parent acids, which are readily available, and these acids are just esterified

using standard procedures. The exception is the amide (3) which starts from the acid and the corresponding amine and the two are heated together.

Compound (12) is prepared from phenol via Friedel Crafts acylation.

For the sulphonamides the synthesis starts from the parent phenol/aniline, etc. by sulphonation with excess of chlorosulphonic acid to yield the sulphonyl chloride which is in turn further reacted with octyl amine to give the desired



sulphonamide. (see example scheme)

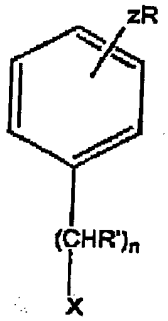
EXAMPLE 3

The following is a formulation according to the present invention. It is made by known processes.

Ingredient	%w/w
70% aq.sorbitol	45.0
Saccharin	0.2
Polyethylene glycol	2.0
Titanium dioxide	1.0
Sodium fluoride	0.32
Thickening silica	9.0
Abrasive silica	10.0
SLS	1.6
Sodium carboxymethylcellulose	0.8
Flavour	1.0
Zinc citrate trihydrate	0.75
n-Octyl gallate	1.0
Water	to 100

CLAIMS

1. An oral composition comprising a compound of Formula 1:



Formula (1),

wherein:

R is a group independently selected from the group consisting of: H, F, Cl, Br, -OH, C_{1-5} alkyl, -C(O)H, $-C(O)C_{1-5}$ alkyl, $-OCH_3$, $-C_2H_5$, $-NH_2$, $-NHC(O)CH_3$ and $C(O)OC_{1-6}$ alkyl and z is from 1 to 5;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', -O-R'', $-SO_2NH$-R'', -OCHR'O-R'' and $-SO_2$-R'';

and R'' is selected from the group consisting of: $-C_{1-16}$ alkyl or $-CH_2C_6H_6$.

and wherein the compound of formula 1 is not a C_{1-16} alkoxy ester of monohydroxybenzoic acid with the hydroxyl group in the para position.

2. An oral composition according to claim 1, wherein X is-C(O)O-R''.

3. An oral composition according to claim 1 or 2, wherein R'' is an aliphatic alkyl group.

4. An oral composition according to any preceding claim, wherein R'' represents a straight chain alkyl group comprising from 5 to 12 carbon atoms.

5. An oral composition according to any preceding claim, wherein -R'' is C_6-C_{12}-alkyl.

6. An oral composition according claim 5, wherein -R'' is C_8-alkyl.

7. An oral composition according to any preceding claim, wherein z is 1.

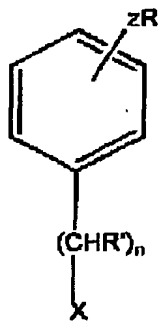
8. An oral composition according to any preceding claim, wherein the compound of formula I is present in the composition in the range of from 0.001 to 5% by weight.

9. Oral composition according to any preceding claim wherein the composition comprises an agent selected from the group consisting of anti-caries agents, anti-

tartar agents, anti-oral malodour agents, tooth whitening agents, breath freshening agents and mixtures thereof.

ABSTRACT

An oral composition comprising a compound of Formula 1:



Formula (1),

wherein:

R is a group independently selected from the group consisting of: H, F, Cl, Br, -OH, C_{1-5} alkyl, -C(O)H, -C(O)C_{1-5} alkyl, $-OCH_3$, $-C_2H_5$, $-NH_2$, $-NHC(O)CH_3$ and C(O)OC_{1-6} alkyl and z is from 1 to 5;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', -O-R'', $-SO_2NH$-R'', -OCHR'O-R'' and $-SO_2$-R'';

and R'' is selected from the group consisting of: $-C_{1-16}$ alkyl or $-CH_2C_6H_6$,

and wherein the compound of formula 1 is not a C_{1-16} alkoxy ester of monohydroxybenzoic acid with the hydroxyl group in the para position.